New Treatments for Fecal Incontinence: Update for the Gastroenterologist

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Fecal incontinence is one of the most emotionally devastating of all nonfatal conditions. Many patients do not respond satisfactorily to conservative measures, and there is a need for new and effective strategies when medical therapy fails. The development of sacral nerve stimulation and other forms of neuromodulation and the injection of biologically compatible substances into the anal sphincter complex have brought renewed enthusiasm for using these novel treatments in this underserved population. Because injectable bulking agents such as dextranomer in stabilized hyaluronic acid can be administered in an outpatient setting, this procedure is being marketed to both gastroenterologists and surgeons. This article reviews both sacral nerve stimulation and dextranomer bulking agents and compares their strengths and potential limitations in patients with fecal incontinence.

Keywords: Sacral Nerve Stimulation; Injectable Anal Bulking Agents; Neuromodulation.

Fecal incontinence is one of the most devastating of all nonfatal conditions, resulting in considerable embarrassment and anxiety to those who suffer from it. It affects 2% to 17% of people living in the community and almost half of all nursing home residents. Many individuals with fecal incontinence are so ashamed that they frequently do not volunteer this complaint to their physicians and must be asked directly. The prevalence of fecal incontinence is comparable in both men and women; it is increased in older age groups, those with poor health status or physical limitations, and individuals residing in nursing homes. Other recognized associations include complications associated with childbirth, certain surgical procedures, the coexistence of diarrhea or irritable bowel syndrome, and specific diseases (Table 1).

The causes of fecal incontinence include a number of broad categories that occur alone or in combination. Many of these are suggested by a careful history and directed physical examination including perianal inspection, digital rectal examination, and a focused neurologic examination of the perineum and lower extremities. Such an examination is heavily dependent on the experience and skills of the examining physician. Unfortunately, it is not taught well at any level of medical training, including gastroenterology fellowship programs. In selected patients, especially when there is diagnostic uncertainty, tests to assess anorectal structure and function may be performed to assess pathogenetic mechanisms.

The major clinical point to emphasize is that fecal incontinence is a disorder that occurs via a number of different mechanisms, not all of which can be characterized by examination and testing. The corollary is that no single treatment approach is appropriate for all patients, and it is incumbent on those who propose a new treatment to identify those patients most likely to benefit on the basis of carefully performed clinical studies.

Fecal incontinence can be subtyped clinically into passive incontinence, which occurs without warning, and urge incontinence, which occurs despite active efforts to retain stool. Contributing factors include structural or functional weakness of the anal sphincters and/or puborectalis muscle, impaired rectal sensation, and reduced colonic and rectal storage capacity. Finally, the consistency and delivery of stool to the anorectum are important; for example, diarrhea and or rapid stool propulsion may uncover subclinical weakness of continence mechanisms. For the clinician, introduction of measures to treat the diarrhea and slow the delivery of stool to the rectum are important components of the conservative management of incontinence. However, many patients do not respond satisfactorily to conservative measures and there is a need for new and effective strategies when medical therapy fails. The need is particularly urgent because traditional surgical approaches are of uncertain efficacy for functional fecal incontinence, even in patients who have documented anal sphincter defects. For example, in short-term studies, up to 85% of patients with incontinence and sphincter defects are improved after overlapping anal sphincteroplasty. However, long-term results have been disappointing, with failure rates of greater than 50% after 40 to 60 months, and even greater deterioration thereafter; this is especially true in older patients.

Abbreviations used in this paper: CCFIS, Cleveland Clinic Fecal Incontinence Severity; FDA, Food and Drug Administration; FIQOL, fecal incontinence-specific quality-of-life; SNS, sacral nerve stimulation.
The development of sacral nerve stimulation (SNS) and other forms of neuromodulation and the injection of biologically compatible substances into the anal sphincter complex have brought renewed interest and enthusiasm for treating this underserved population. Both approaches were extrapolated from their successful use in patients with urinary incontinence to the treatment of fecal incontinence. Because injectable bulking agents such as dextranomer in stabilized hyaluronic acid can be administered in an outpatient office setting and requires no sophisticated skills on the part of the practitioner, this procedure is being marketed aggressively to both gastroenterologists and colorectal surgeons. Therefore, it is important that gastroenterologists become familiar with this technology and other forms of neuromodulation.

### Injections of Dextranomer in Stabilized Hyaluronic Acid for the Treatment of Fecal Incontinence

The concept of injecting a biomaterial to augment anal canal pressures to treat fecal incontinence was first proposed about 2 decades ago; since then, many different substances have been injected with varying results and often using suboptimal investigative designs. There has been renewed interest in injectable bulking agents since the publication of a randomized, sham-controlled study that reported the outcomes of injection of dextranomer in stabilized hyaluronic acid (NASHA Dx; Q-Med AB, Uppsala, Sweden) into the submucosa of the anal canal in 136 patients with fecal incontinence and sham injections in a control group of 70 patients. NASHA Dx has long been used as a bulking agent in urologic procedures with few side effects and there seemed to be biologic plausibility for its use in select patients with fecal incontinence. Although the optimal group of patients intuitively would seem to be those with passive incontinence and low anal canal pressures, the pivotal study, which was performed with input from the Food and Drug Administration (FDA), studied mainly nonobese female patients who were not characterized as having either urge or passive incontinence. The inclusion of patients with urge incontinence seems somewhat counterintuitive because such patients often have weakness of the external anal sphincter as well as decreased rectal capacity and rectal hypersensitivity, none of which would be expected to be altered by an injectable bulking agent. The validated Cleveland Clinic Fecal Incontinence Severity (CCFIS) scale and a fecal incontinence–specific quality-of-life (FIQOL) scale were administered before and after treatment. However, no studies of anorectal sensory or motor functions were performed at any time. This omission deprived the investigators of an opportunity to determine if outcomes correlated with objective improvement in anal canal pressures or other anorectal parameters.

As appears to be the traditional standard for efficacy in studies of fecal incontinence, the primary end point chosen was a 50% or greater decrease in the number of incontinence episodes and a corresponding increase in days free of episodes of incontinence, as assessed over a 2-week period at various predetermined time intervals after treatment. A second injection was permitted in patients who had no improvement within 1 month and, indeed, 80% of patients in the active treatment group required a second injection. Based on these criteria, 53% of patients receiving NASHA Dx vs 32% receiving injection of a sham were classified as responders at 6 months. Curiously, no significant differences in responses were noted at 3 months. Of greater concern, no significant improvements between active and sham patients were noted in 3 of the 4 parts of the FIQOL scale (lifestyle, depression and self-perception, and embarrassment scales) and only a small improvement was noted in the coping and behavior scale. Six percent of treated patients were fully continent at 6 months, although this was not reported in the original report (to my knowledge, no data have been reported for sham-treated patients). Subsequent reports indicated that 11% of the NASHA Dx–treated patients were fully continent at 12 months, a somewhat puzzling finding in that efficacy of most surgical treatments for incontinence tends to diminish with time and it is unclear as to why a bulking agent would continue to improve continence barriers over time. By using 6-month data, one would have to treat 17 patients (with up to 2 injections) to produce 1 fully continent individual (or 9 patients if we use the 1-year results). NASHA Dx was approved by the FDA in 2012 as both safe and effective for the treatment of fecal incontinence and now is being marketed as an office-based treatment to be administered by...
health care providers who have received appropriate technical training for administering the polymer.

**Which Patients Are Optimal Candidates for NASHA Dx or any Other Perianal Injectable Bulking Agent on the Basis of This Study?**

Although there are several possible causes of passive fecal incontinence, the predominant association has been with weakness of the internal anal sphincter (IAS), which is responsible for about 70% of resting anal canal pressure. This may occur because of degeneration of a structurally intact IAS, such as occurs in systemic sclerosis, or damage to the myenteric nerves after radiation therapy or structural damage from sphincterotomy for chronic anal fissure, fistula surgery, hemorrhoidectomy, or trauma during childbirth. Although anorectal manometry can provide objective measurements of resting anal canal pressure, IAS weakness often can be detected by a careful digital examination performed by an experienced clinician. However, the normal range of anal pressures is broad and there is often little correlation between measured resting pressures and passive incontinence. Nevertheless, it would appear biologically plausible that enhancing resting anal canal pressures with an injectable bulking agent might be effective in this group.

Unfortunately, we do not know from the NASHA Dx report if this is so because patients were not categorized clinically or manometrically. Whether NASHA Dx injections even increase anal canal pressures is uncertain because another study of patients with fecal incontinence who received up to 2 injections of NASHA Dx had no increase in resting or squeeze anal canal pressures when studied 6 months after treatment. Moreover, outcomes in this latter study were no better than a comparator group who received a noninvasive intervention of biofeedback. The signal for efficacy in the NASHA Dx study also may have been diluted by the inclusion of patients with urge incontinence or weakness of other continence mechanisms, which would not be enhanced by injection of a bulking agent. It is possible that the 6% to 11% of patients who achieved full continence belonged to the subgroup with passive incontinence, but this is speculative. Therefore, to offer this therapy to patients with urge or mixed incontinence is likely to increase the frequency of unsatisfactory outcomes and engender pessimism among health care providers about offering this treatment. If true, it might deprive patients who are most likely to benefit from such therapy from being offered it.

**What Are the Appropriate Criteria for Efficacy in any Treatment for Fecal Incontinence?**

As previously discussed, the primary concern in any treatment study is the definition of efficacy. In a nonfatal condition such as fecal incontinence, this should include patient satisfaction and enhanced quality of life specifically related to incontinence. The latter was the reason for the development and validation of the symptom-specific FIQOL, which was used in the NASHA Dx study and has become the standard for studies of treatments related to fecal incontinence. This instrument consists of 4 domains: lifestyle (10 questions), coping/behavioral (9 questions), depression (7 questions), and embarrassment (3 questions). Clinical investigators need such instruments to determine if treatment has made a difference (positive or negative) to their patients and, if so, how much. Although a clinician’s orientation is necessary for conducting trials, the patient’s perspective of improvement is essential. Accordingly, if there is a discrepancy between stated efficacy and improvement in quality of life, the criteria for a positive response must be re-examined.

In the NASHA Dx study, more patients treated with NASHA Dx met the primary end point than with sham (P = .0089). However, the median decrease in the number of incontinence episodes at 3 and 6 months was not significantly different from sham, and the mean change in CCFIS did not differ between the 2 groups at 6 months. In addition, the mean CCFIS for the group after treatment with NASHA DX was 10.9 (scale, 0–20), which was above the minimum CCFIS required for entry into the trial. Finally, no differences in lifestyle, depression, self-perception, or embarrassment were noted between treatment and sham groups on the FIQOL.

One possible explanation for this discrepancy may reside in the definition of a response, defined as a 50% or greater reduction in the number of episodes of incontinence. This is very difficult to analyze in the absence of individual baseline data. As an example, if a patient reports having 2 episodes of incontinence daily and after treatment has only 1 episode daily (which would be considered a response), I doubt that most clinicians or patients would be impressed. Nor would I be satisfied if my patient with 6 episodes of incontinence per week experienced a reduction after treatment to 3 per week (also considered a response). I would suggest that these changes do not constitute a clinically important improvement from the patient’s perspective. This may explain, at least in part, why there were little or no changes in the FIQOL.

Another issue is that the amount of fecal leakage should be considered when assessing the severity of fecal incontinence. Only one of the currently available symptom severity instruments for fecal incontinence considers this parameter, which strongly correlated with its impact on quality of life. This instrument was not used in either of the 2 treatments under discussion.

The FDA and, by extension, editors and reviewers of peer-reviewed journals, strongly should consider redefining what constitutes a clinically important response for any treatment of fecal incontinence. This could be performed by re-analyzing the data from the NASHA Dx
trial. One suggestion would be that clinical responses of patients should be stratified into 4 groups, as follows: those with 50% or less improvement, those with more than 50% to less than 75% improvement, 75% but less than complete continence, and those with full continence. FIQOL and CCFIS scores could be analyzed for each group to determine whether there was meaningful improvement in terms of patient (rather than investigator) satisfaction. The results of such an analysis might well lead to a needed revision of standards for efficacy in this field.

This is not to say that NASHA Dx was not effective for any patients with fecal incontinence. However, because of the inclusion criteria and failure to characterize patients into those with passive or urge incontinence, the results are difficult to interpret. There were some patients who did achieve complete continence but the reader/clinician does not know who they are. There is clearly a need for a well-designed study of NASHA Dx to be performed in patients with fecal incontinence who are well-characterized clinically (passive vs urge incontinence), with anorectal measurements and meaningful clinical end points. Unfortunately, once FDA approval occurs, marketing to often poorly informed physicians becomes predominant and further investigation is not rewarded.

**How Does the NASHA Dx Study Compare With Sacral Nerve Stimulation Studies for Fecal Incontinence?**

Sacral neuromodulation was first used to treat neurogenic bladder with urinary incontinence and subsequently was extended to use in patients with fecal incontinence who had failed conservative therapy. Compared with NASHA Dx, the technique requires more sophisticated skills to place a temporary stimulating electrode into a sacral foramen (most often S3). If there is a positive response during a 2-week period, a permanent electrode is connected to a subcutaneously embedded neurostimulator placed in the gluteal area. On the basis of a large North American multicenter trial published in 2010, SNS was approved for use in the treatment of fecal incontinence in the United States by the FDA in 2012. It is interesting to compare this pivotal study with the NASHA Dx study in terms of design, characterization of patients, and definitions of efficacy. It also is important to recognize that the North American study was designed and performed after previous European studies had been published; in contrast, the NASHA Dx study was the first large study that evaluated this particular polymer for fecal incontinence.

In the North American multicenter SNS study, 120 of 133 eligible patients with fecal incontinence responded to the test stimulation and proceeded to chronic stimulation. Patients were categorized as having passive incontinence (41%), urge incontinence (45%), or mixed. All patients underwent anorectal manometry and anal sonography, and completed the FIQOL and a Fecal Incontinence Severity Index. Similar to NASHA Dx, the primary outcome was a 50% or greater reduction of the number of incontinence episodes per week compared with baseline at 12 months after implantation. However, in contrast to NASHA Dx, improvement in weekly incontinent episodes was stratified further as follows: 50% to 75%, more than 75% to less than 100%, and complete continence. At 12 months, 40% of patients had achieved complete continence, 28% had improved by more than 75% to less than 100%, and 14% improved from 50% to 75%. Thus, using a single criteria of a 50% or greater reduction in the number of incontinent episodes, 83% were improved at 12 months compared with baseline. All 4 subscales of the FIQOL significantly improved by 3 months and remained steady through 36 months, but in contrast to the NASHA Dx study, there was no sham comparator group. As expected, there were more adverse effects with SNS, including 26 that were designated as serious, of which a number required removal of the device. This was considered acceptable in view of the magnitude of efficacy. However, because there was no sham control group, there was no blinding of patients or investigators.

**Is the Absence of a Randomized Control Trial a Serious Flaw in Determining Efficacy of Sacral Nerve Stimulation or any Other Novel Treatment for Fecal Incontinence?**

The rationale for the adoption of the placebo- (or sham-) controlled randomized trial was an effort to control for selection and response biases by both subjects and investigators. For example, the NASHA Dx study noted a 32% placebo response using the primary end point of a 50% or greater decrease in incontinence episodes compared with baseline. The investigators in the SNS trial addressed the absence of a sham group and concluded that it seemed unreasonable to attribute the magnitude of benefit (especially the 40% fully continent group) to a placebo effect; some objective observers would be inclined to agree (as were the journal editors and reviewers of the manuscript). Nevertheless, the hope is that all future studies of new treatments for fecal incontinence will include a placebo/sham arm, as the literature is filled with examples of new treatments that are successful in uncontrolled studies but do not differ from or even underperform sham/placebo arms. Another suggestion is that after such trials enroll patients with fecal incontinence, they are first given conservative therapy by specialized therapists and gastroenterologists before concluding that patients have failed therapy. Certainly, it is unclear in both the NASHA Dx and SNS trials how rigorous conservative therapy was before entry into the studies.
What Is the Mechanism by Which Sacral Nerve Stimulation Works in Patients With Fecal Incontinence?

The initial and biologically plausible hypothesis underlying SNS was that it would alter anorectal physiology, perhaps by improving external anal sphincter and/or puborectalis functions that are modulated by sacral motor pathways. However, this has not been shown convincingly in subjects who improve with SNS and underscores that clinical improvement of fecal incontinence may not correlate with anorectal measurements. An alternative explanation has been proposed by a recent study of SNS in 11 patients with urge incontinence. SNS resulted in a substantial increase in retrograde colonic propagating sequences, which did not occur with sham stimulation. This suggests that SNS may improve continence and urgency through alterations of colonic motility rather than having a direct effect on anorectal functions and also reinforces the clinical importance of modulating stool delivery to the anorectum as being paramount in improving urge incontinence in some patients. This may explain favorable reports of SNS given for fecal incontinence after low anterior resection for rectal cancer. If these results are confirmed, SNS conceivably could be indicated in patients who have fecal incontinence associated with decreased rectal storage capacity for different reasons but this has not been shown convincingly. Such a mechanism of action would not be expected after injection of a localized bulking agent.

Should Gastroenterologists Offer NASHA Dx to Patients With Fecal Incontinence and, if so, Which Ones?

In the 136 NASHA Dx–treated patients in the pivotal trial, 2 patients developed an abscess, 14% had proctalgia, and rectal hemorrhage occurred in 7%; only the abscesses were considered serious. In a more recent open-labeled trial, there were 6 abscesses among 115 treated patients, 3 of whom required incision and drainage. Proctalgia and fever rates were similar to those of the pivotal trial. In yet a third trial, abscesses occurred in 3 of the first 10 treated patients, leading the investigators to administer prophylactic antibiotics to the remaining patients. Thus, some complications that may require intervention are to be expected, especially if injections are performed by gastroenterologists with less knowledge of anorectal anatomy than their colorectal counterparts. Furthermore, it should not be assumed that complication rates will be as low as those reported by experienced colorectal surgeons at these study sites. My personal preference would be to have a surgeon with detailed knowledge of the anorectal complex perform these procedures and be responsible for managing any serious complications. Optimally, these patients should be screened and aggressively treated with noninvasive measures before undergoing polymer injections.

The more important question is identifying which patients should be offered injection therapy in clinical practice. I would suggest that only patients who have failed optimal conservative therapy and who show abnormalities that make NASHA Dx biologically plausible should be offered therapy. There should be clear and full disclosure of the existing data to potential candidates for treatment, emphasizing the fact that complete continence has been observed in, at most, 11% of treated patients, and that 2 injections will be needed in the majority of patients. At present, there is no approved billing code for this procedure in all insurance plans so that patients often may have to bear some or all of the cost of treatment. In contrast to patients with urge incontinence who may benefit from biofeedback therapy, those with passive incontinence probably are unsuitable for biofeedback and may be referred for bulking injections if they fail conservative measures. I would target patients with passive incontinence in whom defecatory abnormalities, which may result in retained stool in the rectum, have been excluded with appropriate testing. It is not necessary to select patients strictly on the basis of anal canal pressures, which are imperfect indicators of continence, but it would be of interest to have before and after measurements of resting and squeeze anal canal pressures to document any changes resulting from NASHA Dx. Ideally, such treatments should be offered by individuals who are knowledgeable about anorectal physiology and have appropriate technical skills.

Future Studies

The optimal approach to evaluating NASHA Dx, or any other new therapy, would have been to perform randomized, sham-controlled trials on carefully characterized patients who had undergone at least some physiological studies before and after treatment; more stringent therapeutic end points should have been selected and, indeed, there are data that could be re-analyzed by the investigators to provide a more accurate picture of the true efficacy of NASHA Dx. Carefully performed, methodologically sound studies should be reported before accepting this new and somewhat invasive procedure and marketing it to nonsurgical physicians. I believe that SNS has better supporting data than the use of bulking agents to justify its use in selected patients with fecal incontinence who have failed conservative measures. It also has the advantage that a short-term trial with stimulation can be performed for several weeks before permanent implantation of the electrode and neurostimulator. In contrast, there are less data to support the use of posterior tibial neuromodulation at the present time.

New efficacy end points should be defined in all future studies of fecal incontinence. A 50% reduction in
episodes of incontinence is insufficiently validated in clinical practice unless it can be shown that it has a major impact on patient quality of life and satisfaction. Hopefully, more and better studies will be conducted on all new treatment modalities proposed for the management of fecal incontinence.

References

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Conflicts of interest
The author discloses no conflicts.

1. NASHA treatment for fecal incontinence  
   a. consists of injecting a bulking agent around the external anal sphincter  
   b. results in full continence at 6 months in 1 out of 17 patients treated  
   c. A second injection within a month is required in over half of the patients  
   d. Is not effective for patients with active incontinence

2. Sacral nerve stimulation for fecal incontinence  
   a. consists of an implantable electrode in the sacral region  
   b. 40% of patients achieved complete continence at 12 months  
   c. The benefit was superior than placebo  
   d. Patients who improved clinically had improved anorectal measurement parameters

True or False

3. Sacral nerve stimulation may work by inducing retrograde colonic peristalsis

4. Patients with active incontinence are least likely to respond to biofeedback

5. Rectal abscess is a known complication of NASHA injection, prophylactic antibiotics should probably be used

6. Fecal incontinence is more common in females

7. Passive incontinence occurs without warning, active incontinence occurs despite valiant efforts to retain the stool.

8. Surgical correction of sphincter defects have poor long-term results with failure rates of >50% after 40 to 60 months.

9. There is little correlation between measured resting anal sphincter measurements and passive incontinence

10. NASH injection is probably most effective for patients with passive incontinence